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(74) Agent: MILES, John, S.; Eric Potter Clarkson, Park View House, 58 The Ropewalk, Nottingham NG1 5DD (GB).

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(71) Applicant (*for all designated States except US*): MEDICAL RESEARCH COUNCIL [GB/GB]; 20 Park Crescent, London W1B 1AL (GB).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): JABBOUR, Henry, Nicolas [AU/GB]; MRC Human Reproductive Sciences Unit, Centre for Reproductive Biology, The Chancellor's Building, 49 Little France Crescent, Old Dalkeith Road, Edinburgh EH16 4SB (GB). CRITCHLEY, Hilary, Octavia, Dawn [GB/GB]; Obstetrics and Gynecology, Centre for Reproductive Biology, The Chancellor's Building, 49 Little France Crescent, Old Dalkeith Road, Edinburgh EH16 4SB (GB).

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WO 03/037348 A1

(54) Title: ANTAGONISTS OF PROSTAGLANDIN RECEPTORS EP2 AND/OR EP4 FOR THE TREATMENT OF DYSMENORRHEA AND MENORRHAGIA

(57) Abstract: A method of treating *menorrhagia* and/or *dysmenorrhoea* in a patient the method comprising administering to the patient an antagonist of a prostaglandin EP2 and/or EP4 receptor. Preferably the patient is a human female.

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ANTAGONISTS OF PROSTAGLANDIN RECEPTORS EP2 AND/OR EP4
FOR THE TREATMENT OF DYSMENORRHEA AND MENORRHAGIA

The present invention relates to a method of treatment, in particular a method of treating menorrhagia or dysmenorrhoea.

5

Menorrhagia is over-abundance of the menstrual discharge.

Dysmenorrhoea means painful menstruation.

10 Menorrhagia and dysmenorrhoea affect many women, particularly in the Western world, and represent a significant health problem. At least one in 20 women in the UK aged between 34 and 49 years will consult their general practitioners because of menstrual problems. These women account for more than one in ten of all gynaecological referrals and cost the NHS in 15 excess of £7 million per year for medical prescriptions alone. Perceived abnormal vaginal bleeding is said to account for 70% of the at least 70 000 hysterectomies done each year.

20 At present, the treatments used for menorrhagia include tranexamic acid or mefenamic acid. In severe cases the treatment is hysterectomy (vaginal or abdominal) but this is a major operation with serious morbidity and some risk of death. A review of treatments for menorrhagia is Stirrat (1999) *The Lancet* 353, 2175-2176. The development of further and alternative therapies is desirable.

25

The inventors now propose that an alternative method for treating menorrhagia and/or dysmenorrhoea is to use antagonists of the prostaglandin EP2 and/or EP4 receptor. This approach is believed more

likely to be effective in more women than other drug treatments. The EP2 and/or EP4 receptor antagonists are deliverable *in utero*.

Prostaglandin E₂ elicits its autocrine/paracrine effects on target cells through
5 interaction with transmembrane G protein coupled receptors. To date four
main sub-types of PGE₂ receptors have been identified based on responses
to agonists and antagonists and are pharmacologically divided into EP1,
EP2, EP3 and EP4 which utilise alternate and in some cases opposing
intracellular signalling pathways. EP2 and EP4 increase cAMP levels *via*
10 G_{as}.

The EP2 and EP4 receptors are known to be expressed in human nonpregnant endometrium. No differences in EP2 receptor mRNA expression were detected in tissue collected across the menstrual cycle;
15 however, EP4 receptor mRNA expression was significantly higher in the late proliferative stage than in early, mid and late secretory stage endometrium (Milne *et al* (2001) *J. Clin. Endocrinol. Metab.* 86, 4453-4459. The inventors now show that EP2 and EP4 receptors are overexpressed in women with menorrhagia and in women with menorrhagia
20 and/or dysmenorrhoea it should prove beneficial to treat with receptor antagonists in order to block the signalling pathway and ultimately transcription of target genes that may mediate vascular function/dysfunction and excessive bleeding.

25 The first aspect of the invention provides a method of treating menorrhagia and/or dysmenorrhoea in a patient the method comprising administering to the patient an antagonist of a prostaglandin EP2 and/or EP4 receptor.

It is possible to have menorrhagia and dysmenorrhoea together and the method may be used to treat both conditions in the same patient.

The patient may be any patient who is suffering from menorrhagia and/or dysmenorrhoea or a patient who is at risk from these conditions. Any premenopausal or perimenopausal woman is at risk of menorrhagia and/or dysmenorrhoea; however, menorrhagia is more common at the beginning and end of a woman's reproductive life so typically there is a greater risk when a woman's periods first start and in women over 40 years of age. The patient to be treated may be any female individual who would benefit from such treatment. Typically and preferably the patient to be treated is a human female. However, the methods of the invention may be used to treat female mammals, such as the females of the following species: cows, horses, pigs, sheep, cats and dogs. Thus, the methods have uses in both human and veterinary medicine.

The prostaglandin EP2 receptor antagonist may be any suitable EP2 receptor antagonist. Similarly, the prostaglandin EP4 receptor antagonist may be any suitable EP4 receptor antagonist. By "suitable" we mean that the antagonist is one which may be administered to the patient. The receptor antagonists are molecules which bind to their respective receptors, compete with the natural ligand (PGE_2) and inhibit the initiation of the specific receptor-mediated signal transduction pathways. The receptor antagonists are typically selective to the particular receptor and typically have a higher binding affinity to the receptor than the natural ligand. Although antagonists with a higher affinity for the receptor than the natural ligand are preferred, antagonists with a lower affinity may also be used, but it may be necessary to use these at higher concentrations. Preferably, the antagonists bind reversibly to their cognate receptor. Typically, antagonists

are selective for a particular receptor and do not affect the other receptor; thus, typically, an EP2 receptor antagonist binds the EP2 receptor but does not substantially bind the EP4 receptor, whereas an EP4 receptor antagonist binds the EP4 receptor but does not substantially bind the EP2 receptor.

5 Preferably, the EP2 or EP4 receptor antagonist is selective for the particular receptor subtype. By this is meant that the antagonist has a binding affinity for the particular receptor subtype which is at least ten-fold higher than for at least one of the other EP receptor subtypes. Thus, selective EP4 receptor antagonists have at least a ten-fold higher affinity for the EP4 receptor than
10 any of the EP1, EP2 or EP3 receptor subtypes.

It is particularly preferred that the EP2 or EP4 receptor antagonist is selective for its cognate receptor.

15 The EP2 or EP4 receptor antagonists are typically administered in an effective amount to combat the menorrhagia and/or dysmenorrhoea. Thus, the antagonists may be used to alleviate symptoms (ie are used palliatively) or may be used to treat the condition. The antagonist may be administered prophylactically (and by "treating" we include prophylactic treatment). The
20 antagonist may be administered by any suitable route, and in any suitable form. It is desirable to administer an amount of the EP2 or EP4 receptor antagonist that is effective in preventing or alleviating or ameliorating or curing the menorrhagia and/or dysmenorrhoea.

25 EP2 receptor antagonists include AH6809 (Pelletier *et al* (2001) *Br. J. Pharmacol.* 132, 999-1008).

EP4 receptor antagonists include AH23848B (developed by Glaxo) and AH22921X (Pelletier *et al* (2001) *Br. J. Pharmacol.* 132, 999-1008. The

chemical name for AH23848B is ([1alpha(z), 2beta5alpha]-(+/-)-7-[5-[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxo-cyclopentyl]-4-heptenoic acid) (see Hillock & Crankshaw (1999) *Eur. J. Pharmacol.* 28, 99-108). EP4RA (Li i (2000) *Endocrinology* 141, 2054-61) is an EP(4) -
5 selective ligand (Machwate *et al* (2001) *Mol. Pharmacol.* 60: 36-41). The omega-substituted prostaglandin E derivatives described in WO 00/15608 (EP 1 114 816) (Ono Pharm Co Ltd) bind EP4 receptors selectively and may be EP4 receptor antagonists.

10 Peptides described in WO 01/42281 (Hopital Sainte-Justine) eg: IFTSYLECL, IFASYECL, IFTSAECL, IFTSYEAL, ILASYECL, IFTSTDCL, TSYEAL (with 4-biphenyl alanine), TSYEAL (with homophenyl alanine) are also described as EP4 receptor antagonists, as are some of the compounds described in WO 00/18744 (Fujisawa Pharm Co
15 Ltd). The 5-thia-prostaglandin E derivatives described in WO 00/03980 (EP 1 097 922) (Ono Pharm Co Ltd) may be EP4 receptor antagonists.

EP4 receptor antagonists are also described in WO 01/10426 (Glaxo), WO 00/21532 (Merck) and GB 2 330 307 (Glaxo).

20

WO 00/21532 describes the following as EP4 receptor antagonists:

25 5-butyl-2,4-dihydro-4-[[2'-[N-(3-chloro-2-thiophenecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-2-{2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one potassium salt;

5-butyl-2,4-dihydro-4-[[2'-[N-(2-methyl-3-furoyl)sulfamoyl]biphenyl-4-yl]methyl]-2-{2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one;

5-butyl-2,4-dihydro-4-[[2'-[N-(3-methyl-2-thiophenecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-2-{2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one;

5 5-butyl-2,4-dihydro-4-[[2'-[N-(2-thiophenecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-2-{2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one;

10 5-butyl-2,4-dihydro-4-[[2'-[N-[2-(methypyrrole)carbonyl]sulfamoyl]biphenyl-4-yl]methyl]-2-{2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one.

GB 2 330 307 describes [1 α (Z), 2 β ,5 α]-(\pm)-7-[5-[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid and [1R[1 α (z),2 β ,5 α]]-(-)-7-[5-[(1,1'-biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid.

WO 00/18405 (Pharmagene) describes the EP4 receptor antagonists AH22921 and AH23848 (which are also described in GB 2 028 805 and US 4, 342, 756). WO 01/72302 (Pharmagene) describes further EP4 receptor antagonists, for example those described by reference to, and included in the general formula (I) shown on page 8 *et seq.*

All of these references to EP2 and EP4 receptor antagonists are incorporated herein by reference.

25 It will be appreciated that one or more EP2 receptor antagonists, or one or more EP4 receptor antagonists, may be administered to the patient. It will also be appreciated that a combination of one or more EP2 or EP4 receptor

antagonists may be administered to the patient. Preferably, an EP4 receptor antagonist is administered to the patient.

A second aspect of the invention provides the use of an antagonist of a prostaglandin EP2 and/or EP4 receptor in the manufacture of a medicament for treating menorrhagia and/or dysmenorrhoea.

A third aspect of the invention provides the use of an antagonist of a prostaglandin EP2 and/or EP4 receptor in treating menorrhagia and/or dysmenorrhoea.

A fourth aspect of the invention provides an antagonist of a prostaglandin EP2 and/or EP4 receptor for treating menorrhagia and/or dysmenorrhoea.

The aforementioned EP2 or EP4 receptor antagonists, or a formulation thereof, may be administered by any conventional method including oral and parenteral (eg subcutaneous or intramuscular) injection. The treatment may consist of a single dose or a plurality of doses over a period of time.

While it is possible for a compound of the invention to be administered alone, it is preferable to present it as a pharmaceutical formulation, together with one or more acceptable carriers. The carrier(s) must be "acceptable" in the sense of being compatible with the compound of the invention and not deleterious to the recipients thereof. Typically, the carriers will be water or saline which will be sterile and pyrogen free.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the antagonist with the

carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

5

Formulations in accordance with the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a 10 non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or 15 more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (eg povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (eg sodium starch glycolate, cross-linked povidone, cross-linked 20 sodium carboxymethyl cellulose), surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, 25 hydroxypropylmethylcellulose in varying proportions to provide desired release profile.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavoured basis, usually sucrose and

acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouth-washes comprising the active ingredient in a suitable liquid carrier. Buccal administration is also preferred.

5

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose or an appropriate fraction thereof, of an active ingredient.

20

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

25 Certain EP2 and EP4 receptor antagonists are proteins or peptides. Proteins and peptides may be delivered using an injectable sustained-release drug delivery system. These are designed specifically to reduce the frequency of

injections. An example of such a system is Nutropin Depot which encapsulates recombinant human growth hormone (rhGH) in biodegradable microspheres that, once injected, release rhGH slowly over a sustained period.

5

The protein and peptide can be administered by a surgically implanted device that releases the drug directly to the required site. For example, Vitraser releases ganciclovir directly into the eye to treat CMV retinitis. The direct application of this toxic agent to the site of disease achieves 10 effective therapy without the drug's significant systemic side-effects.

Electroporation therapy (EPT) systems can also be employed for the administration of proteins and peptides. A device which delivers a pulsed electric field to cells increases the permeability of the cell membranes to the 15 drug, resulting in a significant enhancement of intracellular drug delivery.

Proteins and peptides can be delivered by electroincorporation (EI). EI occurs when small particles of up to 30 microns in diameter on the surface of the skin experience electrical pulses identical or similar to those used in 20 electroporation. In EI, these particles are driven through the stratum corneum and into deeper layers of the skin. The particles can be loaded or coated with drugs or genes or can simply act as "bullets" that generate pores in the skin through which the drugs can enter.

25 An alternative method of protein and peptide delivery is the ReGel injectable system that is thermo-sensitive. Below body temperature, ReGel is an injectable liquid while at body temperature it immediately forms a gel reservoir that slowly erodes and dissolves into known, safe, biodegradable

polymers. The EP2 or EP4 receptor antagonist is delivered over time as the biopolymers dissolve.

5 Protein and peptide pharmaceuticals can also be delivered orally. The process employs a natural process for oral uptake of vitamin B₁₂ in the body to co-deliver proteins and peptides. By riding the vitamin B₁₂ uptake system, the protein or peptide can move through the intestinal wall. Complexes are synthesised between vitamin B₁₂ analogues and the drug that retain both significant affinity for intrinsic factor (IF) in the vitamin B₁₂ 10 portion of the complex and significant bioactivity of the drug portion of the complex.

15 Proteins and polypeptides can be introduced to cells by "Trojan peptides". These are a class of polypeptides called penetratins which have translocating properties and are capable of carrying hydrophilic compounds across the plasma membrane. This system allows direct targetting of oligopeptides to the cytoplasm and nucleus, and may be non-cell type specific and highly efficient. See Derossi *et al* (1998), *Trends Cell Biol* 8, 84-87.

20

The antagonist is administered at a dose (or in multiple doses) which produces a beneficial therapeutic effect in the patient. Suitable doses may be determined by the physician. The dose to be administered is determined upon age, body weight, mode of administration, duration of the treatment, 25 and pharmacokinetic and toxicological properties of the antagonist.

It is preferred if the antagonist is administered orally. It is further preferred if the antagonist is administered to the female reproductive system. For example, the antagonist may suitably be administered intravaginally using,

for example, a gel or cream or vaginal ring or tampon. The antagonist may also advantageously be administered using an intrauterine device.

Typically, the gel or cream is one which is formulated for administration to
5 the vagina. It may be oil based or water based. Typically, the antagonist is present in the cream or gel in a sufficient concentration so that an effective amount is administered in a single (or in repeated) application.

Typically, the vaginal ring comprises a polymer which formed into a
10 "doughnut" shape which fits within the vagina. The antagonist is present within the polymer, typically as a core, which may dissipate through the polymer and into the vagina and/or cervix in a controlled fashion. Vaginal rings are known in the art. The vaginal ring may be disposable and is retained intravaginally during the woman's period and therefore contains
15 sufficient antagonist to be released and to be effective during the woman's period. Alternatively, the vaginal ring may be used over a time interval of around three months to one year, during which time sufficient antagonist is released to have a beneficial effect over that period of time. It will be appreciated that the polymer from which the ring is made, the size and
20 shaper of the ring and the content of antagonist, as well as other parameters, may be selected by reference to whether the ring is for use in one cycle or for longer spells.

Typically, the tampon is impregnated with the antagonist and that a
25 sufficient amount of the antagonist is present in the tampon bearing in mind that more than one tampon is generally used in a single day, for example up to 10 to 15 tampons in a single day.

Typically, the intrauterine device is for placing in the uterus over extended periods of time, such as between one and five years. Typically, the intrauterine device comprises a plastic frame, often in the shape of a "T" and contains sufficient antagonist to be released over the period of use. The 5 antagonist is generally present within or encompassed by a slow-release polymer which forms part of the device, such as in the form of a "sausage" of antagonist which wraps around the long arm of the "T" which is typically covered with a controlled-release membrane. Intrauterine devices are known in the art.

10

The invention also provides combinations (such as in a pharmaceutical formulation) of one or more EP2 and/or EP4 receptor antagonists and one or more agents presently used to treat menorrhagia, such as tranexamic acid or mefenamic acid.

15

The invention will now be described in more detail with reference to the following non-limiting Examples and Figure.

Figure 1 shows endometrial sections from menorrhagic and control women 20 stained with antibodies to the EP2 receptor and EP4 receptor as described in Example 2.

Example 1: Expression of EP2 and EP4 receptors in uterine tissue of women with menorrhagia compared to women with no menorrhagia

25

Uterine tissue is collected by biopsy from women with known indication of menorrhagia and/or dysmenorrhoea and women who have normal uterine function. The tissue is assessed for the expression of EP receptors including EP2 and EP4. This is assessed using various molecular techniques. The

signalling of these receptors in response to PGE₂ is assessed. Tissue is cultured for various time in the presence or absence of PGE₂ and the second messenger cAMP is measured in response to these treatments.

5 Expression of EP2 and/or EP4 receptors is elevated in the uterine tissue that comes from women with a known history with menorrhagia and/or dysmenorrhoea. Moreover, the signalling events in response to PGE₂ is augmented in these patients.

10 Hence in women with these conditions, it should prove beneficial to treat with receptor antagonists in order to block the signalling pathway and ultimately transcription of target genes that may mediate vascular function/dysfunction and excessive bleeding.

15 **Example 2: Elevated expression of EP2 and EP4 receptors in endometrium of menorrhagic women compared to control women**

Methods

20 Endometrial sections (5 µm) collected from two women classed as control (with <80 ml blood loss per cycle) or menorrhagic (with >80 ml blood loss per cycle) were dewaxed in xylene and rehydrated using decreasing grades of ethanol. After rinsing in PBS, endogenous peroxidase activity was quenched with 3% H₂O₂ in methanol. Non-immune swine serum (10% serum in PBS) was applied for 20 min before overnight incubation at 4°C with primary antibody. An avidin-biotin peroxidase detection system was then applied (DAKO Ltd, UK) with 3,3'-diaminobenzidine (DAB) as the chromagen. Sections were counter stained with Harris's haematoxylin before mounting. The primary antibodies used in this study were raised in

25

rabbits against human EP2 or EP4 receptor peptide sequences (Cayman Chemicals, USA). The antibody was used at a 1:250 dilution. All treatments were carried out at room temperature unless otherwise specified.

5 *Results*

Staining for both EP2 and EP4 receptors was localised in the glandular epithelial cells and endothelial cells. Lower intensity of staining was observed in the endometrial samples collected from the woman with normal 10 bleeding pattern as compared with endometrium collected with women suffering from menorrhagia. This indicates a higher expression pattern of the two receptors in the latter group of women.

The results are shown in Figure 1.

15

Example 3: Treatment of menorrhagia with an EP2 receptor antagonist

A woman presents to her physician with symptoms of menorrhagia. The 20 physician diagnoses menorrhagia. The woman is administered an effective dose of AH6809.

Example 4: Treatment of dysmenorrhoea with an EP4 receptor antagonist

25

A woman presents to her physician with symptoms of dysmenorrhoea. The physician diagnoses dysmenorrhoea. The woman is administered an effective dose of AH22921.

Example 5: Suppository

	<u>mg/suppository</u>
AH22921 (63 µm)*	250
Hard Fat, BP (Witepsol H15 - Dynamit Nobel)	1770
	5
	2020

*The antagonist AH22921 is used as a powder wherein at least 90% of the particles are of 63 µm diameter or less.

10

One fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200 µm sieve and added to the molten base with mixing, using a silverson fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining Witepsol H15 is added to the suspension and stirred to ensure a homogenous mix. The entire suspension is passed through a 250 µm stainless steel screen and, with continuous stirring, is allowed to cool to 40°C. At a temperature of 38°C to 40°C 2.02 g of the mixture is filled into suitable plastic moulds. The suppositories are allowed to cool to room temperature.

15

Example 6: Pessaries

	<u>mg/pessary</u>
AH23848B	250
Anhydrate Dextrose	380
Potato Starch	363
Magnesium Stearate	7

20

The above ingredients are mixed directly and pessaries prepared by direct compression of the resulting mixture.

Example 7: Vaginal ring

5

A vaginal ring containing 5-butyl-2,4-dihydro-4-[[2'-[N-(3-chloro-2-thiophenecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-2-{2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one potassium salt; is produced using core extrusion technology.

10

Example 8: Intrauterine device

An intrauterine device containing AH6809 is produced using standard technology.

15

Example 9: Tampon

A tampon for treating menorrhagia and/or dysmenorrhoea is produced by impregnating a standard tampon with an effective dose of 5-butyl-2,4-dihydro-4-[[2'-[N-[2-(methypyrrole)carbonyl]sulfamoyl]biphenyl-4-yl]methyl]-2-{2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one.

CLAIMS

1. A method of treating menorrhagia and/or dysmenorrhoea in a patient
the method comprising administering to the patient an antagonist of a
prostaglandin EP2 and/or EP4 receptor.
5
2. A method according to Claim 1 comprising administering an
antagonist of a prostaglandin EP2 receptor.
- 10 3. A method according to Claim 1 comprising administering an
antagonist of a prostaglandin EP4 receptor.
4. A method according to any one of Claims 1 to 3 wherein the patient
premenopausal or perimenopausal.
- 15 5. A method according to Claim 1 wherein the patient is administered
any one or more of AH6809, an omega-substituted prostaglandin E
derivative described in WO 00/15608 (Ono Pharm Co Ltd),
AH23848B, AH22921X, IFTSYLECL, IFASYECL, IFTSAECL,
20 IFTSYEAL, ILASYECL, IFTSTDCL, TSYEAL (with 4-
biphenylalanine), TSYEAL (with homophenylalanine), a 5-thia-
prostaglandin E derivative described in WO 00/03980 (Ono Pharm
Co Ltd), 5-butyl-2,4-dihydro-4-[[2'-[N-(3-chloro-2-
thiophenecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-2-{2-
25 (trifluoromethyl)phenyl]-1,2,4-triazol-3-one potassium salt, 5-butyl-
2,4-dihydro-4-[[2'-[N-(2-methyl-3-furoyl)sulfamoyl]biphenyl-4-
yl]methyl]-2-{2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one,
butyl-2,4-dihydro-4-[[2'-[N-(3-methyl-2-
thiophenecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-2-{2-

(trifluoromethyl)phenyl]-1,2,4-triazol-3-one, 5-butyl-2,4-dihydro-4-[[2'-[N-(2-thiophenecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-2-{2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one, and 5-butyl-2,4-dihydro-4-[[2'-[N-[2-(methypyrrole)carbonyl]sulfamoyl]biphenyl-4-yl]methyl]-2-{2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one.

- 5 6. A method according to Claim 2 wherein the EP2 receptor antagonist is any one or more of AH6809.
- 10 7. A method according to Claim 3 wherein the EP4 receptor antagonist is any one or more of AH23848B, AH22921X, IFTSYLECL, IFASYECL, IFTSAECL, IFTSYEAL, ILASYECL, IFTSTDCL, TSYEAL (with 4-biphenylalanine), TSYEAL (with homophenylalanine), and 5-thia-prostaglandin E derivatives described in WO 00/03980 (Ono Pharm Co Ltd), 5-butyl-2,4-dihydro-4-[[2'-[N-(3-chloro-2-thiophenecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-2-{2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one potassium salt, 5-butyl-2,4-dihydro-4-[[2'-[N-(2-methyl-3-furoyl)sulfamoyl]biphenyl-4-yl]methyl]-2-{2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one, 5-butyl-2,4-dihydro-4-[[2'-[N-(2-thiophenecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-2-{2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one, 5-butyl-2,4-dihydro-4-[[2'-[N-(2-thiophenecarbonyl)sulfamoyl]biphenyl-4-yl]methyl]-2-{2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one, and 5-butyl-2,4-dihydro-4-[[2'-[N-[2-(methypyrrole)carbonyl]sulfamoyl]biphenyl-4-yl]methyl]-2-{2-(trifluoromethyl)phenyl]-1,2,4-triazol-3-one.
- 15 20 25

8. Use of an antagonist of a prostaglandin EP2 and/or EP4 receptor in the manufacture of a medicament for treating menorrhagia and/or dysmenorrhoea.

5 9. Use of an antagonist of a prostaglandin EP2 and/or EP4 receptor in treating menorrhagia and/or dysmenorrhoea.

10. An antagonist of a prostaglandin EP2 and/or EP4 receptor for treating menorrhagia and/or dysmenorrhoea.

10

11. A vaginal ring or a tampon or an intrauterine device comprising an EP2 and/or an EP4 receptor antagonist.

12. A combination of any one or more of an EP2 and/or EP4 receptor antagonist and a further agent used to treat menorrhagia and/or dysmenorrhoea.

15

13. A combination according to Claim 12 wherein the further agent is tranexamic acid or mefenamic acid.

20

14. A pharmaceutical composition comprising a combination according to Claims 12 or 13 and a pharmaceutically acceptable carrier.

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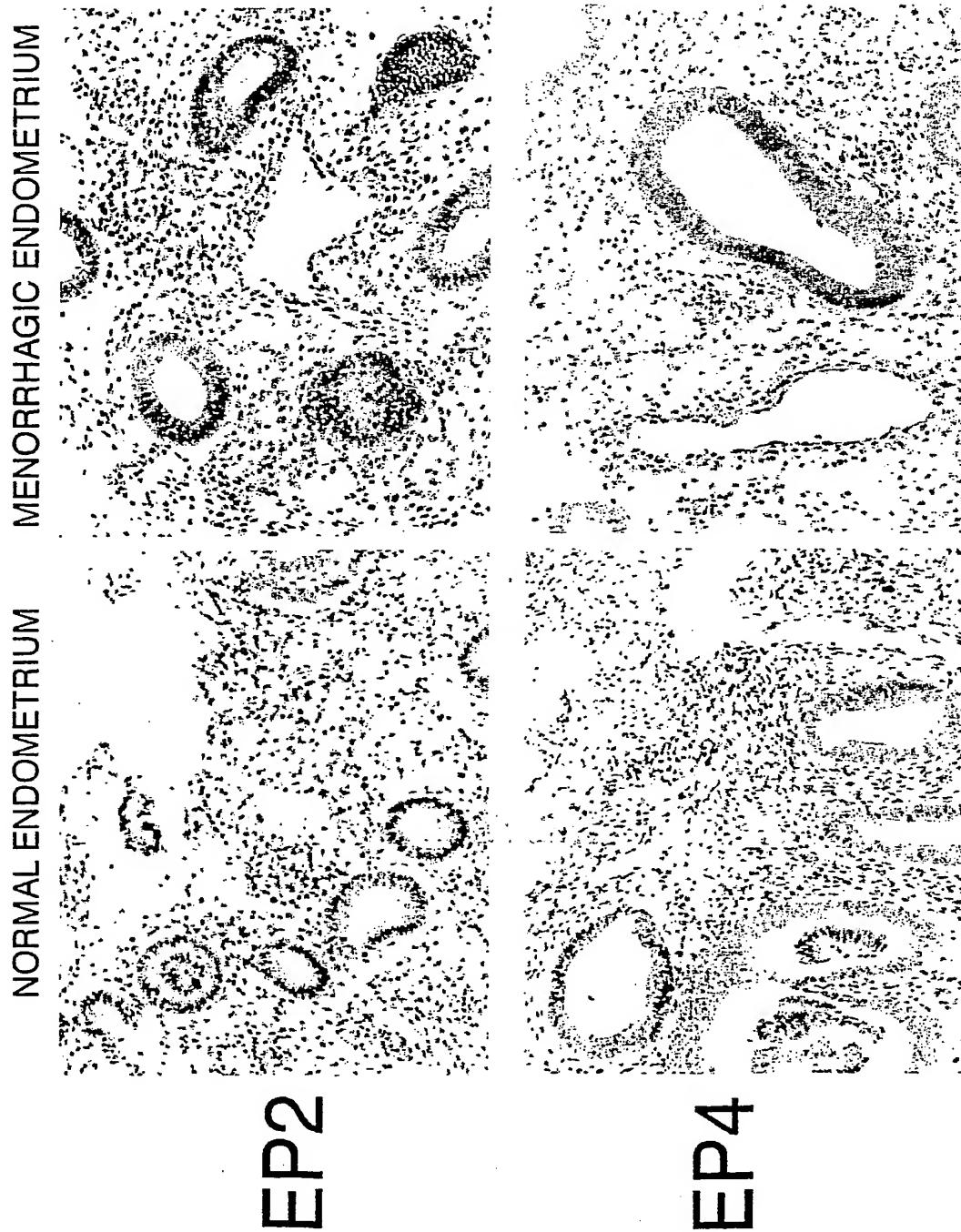


FIGURE 1

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SUBSTITUTE SHEET (RULE 26)

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/Gb 02/04845

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/5375 A61K31/4196 A61K38/08 A61K31/557 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
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BIOSIS, MEDLINE, EPO-Internal, WPI Data, CHEM ABS Data
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C. DOCUMENTS CONSIDERED TO BE RELEVANT
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Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 72302 A (BAXTER GORDON SMITH ;COLEMAN ROBERT ALEXANDER (GB); PHARMAGENE LAB) 4 October 2001 (2001-10-04) cited in the application the whole document	10
Y	---	1-14
X	WO 01 10426 A (GIBLIN GERARD MARTIN PAUL ;GLAXO GROUP LTD (GB); CLAYTON NICHOLAS) 15 February 2001 (2001-02-15) cited in the application page 1, line 10 -page 8, line 20	10
Y	---	1-14
X	GB 2 330 307 A (GLAXO GROUP LTD) 21 April 1999 (1999-04-21) cited in the application	10
Y	page 2, paragraph 2 - paragraph 3 ---	1-14
		-/-

<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.
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<input checked="" type="checkbox"/> Patent family members are listed in annex.
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* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report
--

30 January 2003

14/03/2003

Name and mailing address of the ISA

Authorized officer

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Giacobbe, S

INTERNATIONAL SEARCH REPORT

Internati	Application No
PCT/GB 02/04845	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 18405 A (BAXTER GORDON SMITH ; COLEMAN ROBERT ALEXANDER (GB); PHARMAGENE LAB) 6 April 2000 (2000-04-06) abstract ---	10
Y	WO 01 42281 A (CHEMTOB SYLVAIN ; PERI KRISHNA G (CA); HOPITAL SAINTE JUSTINE (CA)) 14 June 2001 (2001-06-14) page 4, line 5 -page 7, line 9 claim 5 ---	1-14
X	EP 1 097 922 A (ONO PHARMACEUTICAL CO) 9 May 2001 (2001-05-09) claims 1-21 ---	10
Y	MACHWATE M ET AL: "Prostaglandin receptor EP4 mediates the bone anabolic effects of PGE2." MOLECULAR PHARMACOLOGY, vol. 60, no. 1, July 2001 (2001-07), pages 36-41, XP002229205 ISSN: 0026-895X cited in the application abstract ---	1-14
X	LI XIAODONG ET AL: "Knockout of the murine prostaglandin EP2 receptor impairs osteoclastogenesis in vitro." ENDOCRINOLOGY, vol. 141, no. 6, June 2000 (2000-06), pages 2054-2061, XP002229451 ISSN: 0013-7227 abstract ---	10
Y	US 6 211 221 B1 (PETERSON JOHNNY W ET AL) 3 April 2001 (2001-04-03) column 1, paragraph 3 column 2, paragraph 1 -column 3, paragraph 3 ---	1-14
Y	US 5 912 006 A (ERLITZ MARC D ET AL) 15 June 1999 (1999-06-15) column 1, paragraph 3 ---	1-14
		-/-

INTERNATIONAL SEARCH REPORT

Internati	Application No
PCT/GB 02/04845	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HILLOCK C J ET AL: "Inhibitory prostanoid EP receptors in human non-pregnant myometrium." EUROPEAN JOURNAL OF PHARMACOLOGY. NETHERLANDS 28 JUL 1999, vol. 378, no. 1, 28 July 1999 (1999-07-28), pages 99-108, XP002229207 ISSN: 0014-2999 cited in the application abstract page 104, paragraph 3 page 105, paragraph 4 ---	1-14
Y	FRASER I S ET AL: "LONG-TERM TREATMENT OF MENORRHAGIA WITH MEFENAMIC-ACID" OBSTETRICS AND GYNECOLOGY, vol. 61, no. 1, 1983, pages 109-112, XP009004913 ISSN: 0029-7844 the whole document ---	12-14
Y	DUNN C J ET AL: "TRANEXAMIC ACID A REVIEW OF ITS USE IN SURGERY AND OTHER INDICATIONS" DRUGS, ADIS INTERNATIONAL LTD, AT, vol. 57, no. 6, June 1999 (1999-06), pages 1005-1032, XP008005661 ISSN: 0012-6667 page 102, paragraph 4.5 ---	12-14
Y	US 6 197 327 B1 (HARRISON DONALD C ET AL) 6 March 2001 (2001-03-06) the whole document claim 1 ---	11
A	STIRRAT GORDON M: "Choice of treatment for menorrhagia." LANCET (NORTH AMERICAN EDITION), vol. 353, no. 9171, 26 June 1999 (1999-06-26), pages 2175-2176, XP002229208 ISSN: 0099-5355 cited in the application the whole document ---	1-14

INTERNATIONAL SEARCH REPORT

Inte
nal application No.
PCT/GB 02/04845

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 02/04845

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0172302	A 04-10-2001	WO	0172302 A1	04-10-2001
		AU	3445100 A	08-10-2001
		EP	1267867 A1	02-01-2003
WO 0110426	A 15-02-2001	AU	6836200 A	05-03-2001
		WO	0110426 A2	15-02-2001
		EP	1202730 A2	08-05-2002
GB 2330307	A 21-04-1999	NONE		
WO 0018405	A 06-04-2000	WO	0018405 A1	06-04-2000
		AU	9177698 A	17-04-2000
		CA	2345248 A1	06-04-2000
		EP	1115404 A1	18-07-2001
		GB	2341799 A ,B	29-03-2000
		JP	2002525327 T	13-08-2002
WO 0142281	A 14-06-2001	AU	2134001 A	18-06-2001
		WO	0142281 A1	14-06-2001
		EP	1244693 A1	02-10-2002
EP 1097922	A 09-05-2001	AU	4651899 A	07-02-2000
		BR	9912813 A	02-05-2001
		CA	2336952 A1	27-01-2000
		EP	1097922 A1	09-05-2001
		JP	3174563 B2	11-06-2001
		NO	20010213 A	15-03-2001
		US	6462081 B1	08-10-2002
		CN	1312796 T	12-09-2001
		WO	0003980 A1	27-01-2000
		JP	2001089444 A	03-04-2001
		TR	200100623 T2	21-06-2001
US 6211221	B1 03-04-2001	NONE		
US 5912006	A 15-06-1999	WO	0074632 A2	14-12-2000
		AU	4547599 A	28-12-2000
US 6197327	B1 06-03-2001	AU	735407 B2	05-07-2001
		AU	7697698 A	30-12-1998
		BR	9810089 A	08-08-2000
		EP	0988009 A1	29-03-2000
		JP	2002515069 T	21-05-2002
		NZ	502120 A	26-04-2002
		NZ	508130 A	01-03-2002
		WO	9856323 A1	17-12-1998
		US	6086909 A	11-07-2000
		US	6416779 B1	09-07-2002
		CN	1263454 T	16-08-2000

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